UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,434	11/26/2003	Pingyu Zhong	26050-709.501	8676

210 7590 10/15/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	
MAIL DATE	**DELIVERY MODE**
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,434	ZHONG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 13-49* is/are pending in the application.

4a) Of the above claim(s) *13-27 and 29-32* is/are withdrawn from consideration.

5)☒ Claim(s) *28 and 33-35* is/are allowed.

6)☒ Claim(s) *40 and 45-49* is/are rejected.

7)☒ Claim(s) *7-9,36-39 and 41-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 07/23/2007, and a response to the arguments is set forth.

2. Claims 1-6 and 10-12 have been cancelled.

3. Claims 7-9 have been amended.

4. Claims 36-49 have been newly added.

5. Claims 7-9, 28 and 33-49 are under examination.

Objections Withdrawn

6. The objection of the disclosure is withdrawn in view of amendments to the specification.

Rejections Withdrawn

7. The rejection of claims 2-6 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of amendments to the claims. The claims have been cancelled.

8. The rejection of claims 1 and 7-12 under 35 U.S.C. 102(b) as being anticipated by Baca et al (WO 98/45331, International Publication Date: 10/15/1998; IDS – 03/27/2006) is withdrawn in view of amendments to the claims.

New Grounds of Rejections

Claim Objections

9. Claims 7-9, 36-39 and 42-44 is objected to because of the following informalities:

Claims 7-9, 37-39 and 42-44 are objected because the claims recite "... is in a form of ..." which renders the claim confusing. The applicant is suggested to amend to the claims to recite "... is a ..." instead, to obviate this objection.

Claim 36 is objected to because of the recitation "... has a VL domain consisting ... in combination with a VL domain ...". The applicant is recommended to amend the "VL" in line 2 of the claim to recite "VH".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 40 and 45-49 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibodies and antigen-binding fragments thereof comprising all six CDRs, three from the VH domain and three from the VL domain, does not reasonably provide enablement for anti-VEGF antibodies that do not consists of all six CDRs (as in claims 40 and 45-47) or a VH domain or a VL domain (as in claims 48 and 49). The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to a monoclonal antibody that specifically binds to a human VEGF and has a light chain variable domain comprising CDR1, CDR2 and CDR3 regions consisting of the amino acid sequences set forth SEQ ID NOs:172, 195 and 212, respectively (claim 40); a monoclonal antibody that specifically binds to a human VEGF and has a VL comprising CDRR1, CDR2 and CDR3 regions consisting of the amino acid sequences set forth SEQ ID NOs:170, 195 and 214, respectively (claim 45); a monoclonal antibody that specifically binds to a human VEGF and has a heavy chain variable domain comprising CDRR1, CDR2 and CDR3 regions consisting of the amino acid sequences set forth SEQ ID NOs:31, 152 and 327, respectively (claim 46); a monoclonal antibody that specifically binds to a human VEGF and has a VL comprising

CDRR1, CDR2 and CDR3 regions consisting of the amino acid sequences set forth SEQ ID NOs:182, 201 and 222, respectively (claim 47); a VH domain consisting of an amino acid sequence selected from SEQ ID NOs: 88, 90, 91, 106, 107, 107 and 109 (claim 48) and VL domain consisting of amino acid sequence selected from SEQ ID NOs:26, 28 and 36 (claim 49). Thus, the claims broadly encompass antibodies that do not contain a full set of 6 CDRs from the heavy chain variable (VH) domain and the light chain variable (VL) domain as well as Vh domains and VL domains that do not bind VEGF.

BB 10/11/07

The specification discloses only antibodies that specifically bind VEGF and comprise all 6 CDRs, three from the VH domain and three from the VL domain; and antibodies that comprise VH and VL (see pages 22-28, in particular). The specification does not teach anti-VEGF antibodies that do not contain all six CDRs, three from the VH domain and three from the VL domain that bind VEGF or just a VH or VL domain that bind to VEGF. There are no working examples of such antibodies that bind VEGF.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It

is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that humanized antibodies which do not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite VEGF binding function.

The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing humanized antibodies comprising less than all six CDRs that bind VEGF or an antibody VH or VL. The specification provides no direction or guidance regarding how to produce the myriad of antibodies. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must

bear a reasonable correlation with the scope of enablement. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Additionally, Bendig M. M. (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). Thus, the state of the art recognized that it would be highly unpredictable that a humanized molecule or antibody comprising an antibody variable region but comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding antigen or VEGF includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from the same parental antibody in the context of framework sequences which maintain their correct spatial orientation have the requisite antigen-binding function. While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different

antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 307:198-205, 2003), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing humanized antibodies comprising less than six CDRs or a VH or VL domain that bind VEGF. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. Undue

experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by the references cited above, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed humanized antibodies that bind VEGF with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed antibodies bind VEGF, commensurate in scope with the claimed invention.

Conclusion

12. Claims 28 and 33-35 are found allowable.

Claim 41 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
(571) 272-8789

DAVID J. BLANCHARD
~~PATENT~~ PRIMARY EXAMINER